Is the Way Up the Way Forward? Radiotherapy Dose Escalation for Non-small Cell Lung Cancer

David Ball, MB, BS, MD, FRANZCR

(*J Thorac Oncol.* 2006;1: 107–108)

The classical survival curves produced by Puck and Marcus[1] 50 years ago, demonstrating decreasing clonogenic survival with increasing doses of radiation, have become a cornerstone of modern clinical radiobiology, underpinning the notion that for epithelial cancers, escalating the radiotherapy dose increases the probability of local cure, and that the only obstacle to achieving this is the tolerance of the incidentally irradiated adjacent normal tissues.

In the case of non-small cell lung cancer (NSCLC), the evidence for a dose-response relationship is provided by the Radiation Therapy Oncology Group's landmark trial 73-01, which demonstrated superior response rates in patients randomized to a dose of 60 Gy compared with lower doses.[2] This did not, however, translate into longer survival, and there is only limited evidence suggesting a dose-survival relationship up to 60 Gy, including our own non-randomized experience.[3] Nevertheless, 60 Gy, conventionally fractionated, is generally safe and has become a universal standard of care for inoperable NSCLC.

Recent advances in radiation therapy technology, such as three-dimensional (3D) treatment planning, respiratory gating, intensity-modulated radiotherapy, and F18-deoxyglucose positron emission tomography-assisted tumor volume definition, all of which allow the creation of a radiation dose envelope that conforms more closely to the shape of the cancer, have opened up opportunities for reducing the dose to the surrounding healthy tissues, theoretically allowing dose escalation beyond 60 Gy while not exceeding those dose constraints traditionally applied to organs at risk.

In this issue of the journal, Urbanic et al. report the use of 3D techniques to deliver a dose of 80.5 Gy in a cohort of patients with early-stage NSCLC. So as not to unduly prolong overall treatment time, a potential cause of treatment failure, the radiotherapy was delivered as 2.3-Gy fractions. The volume of normal tissue irradiated was further limited by not electively irradiating mediastinal lymph nodes. Although many of the patients had severe co-morbidities that typically represent competing risks for death in a population of this kind, the major cause of death was still NSCLC, and local progression was the dominant cause of failure. Why are these results so disappointing? There is always a danger that, in minimizing the dose to the surrounding tissues, the margins on the tumor become too tight, and there is the potential for geographic miss, particularly if allowance is not made for internal organ motion resulting from the cardiac and respiratory cycles, as seemed to be the case in this study.

Urbanic et al. have nevertheless demonstrated the feasibility of delivering doses well in excess of the 60-Gy benchmark, thereby confirming other reports that dose escalation using 3D techniques is not associated with excessive short- or medium-term toxicity.[4–6] Unfortunately, none of these studies was randomized, and interpretation of the outcomes is further complicated by the requirement that dose escalation to the highest levels is

Department of Radiation Oncology, Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia.
Address correspondence to: David Ball, MB, BS, MD, FRANZCR, Chair, Lung Service, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett St, Melbourne, Victoria, 8006, Australia.

ISSN: 1556-0864/06/0102-0107

usually only possible with the smallest tumors, which may have an inherently better prognosis. Although researchers at the University of Michigan[4] and Memorial SloanKettering[5] have recently reported an apparent improvement in survival associated with dose escalation, this was not the experience of the Radiation Therapy Oncology Group.[6]

We should also not forget that superior outcomes can sometimes be achieved with lower doses of radiotherapy by shortening overall treatment time in the case of continuous hyperfractionated accelerated radiotherapy[7] or in the case of esophageal cancer, for example, by the addition of concomitant chemotherapy.[8]

Investigators designing radiotherapy studies for NSCLC are currently spoiled for choice in regard to promising new strategies that include, in addition to dose escalation, shortening overall treatment time and the concomitant administration of new chemotherapeutic and biological agents. To evaluate the contribution each of these might make individually or in combination to reduce the depressingly high rate of local failure in patients irradiated for NSCLC will be a challenge requiring carefully designed and conducted randomized trials. The fact that we can dose escalate is not sufficient evidence that it works.

REFERENCES

1. Puck TT, Marcus PI. Action of x-rays on mammalian cells. *J Exp Med* 1956;103:653–666.
2. Perez CA, et al. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung: Preliminary report by the Radiation Therapy Oncology Group *Cancer* 1980;45:2744–2753.
3. Ball D, et al. Longer survival with higher doses of thoracic radiotherapy in patients with limited non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1993;25:599–604.
4. Kong FM, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: Long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys* 2006;63:324–333.
5. Rosenzweig KE, et al. Results of a phase I dose-escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable nonsmall cell lung carcinoma. *Cancer.* 2006;103(10):2118–27.
6. Bradley J, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys.* 2006;61(2):318–28.
7. Saunders M, et al. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. *Radiother Oncol.* 1999;52(2):137–48.
8. Herskovic A, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med.* 1992;326(24):1593–8.